PATENT SPECIFICATION

681,712

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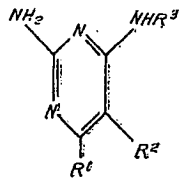
COMPLETE SPECIFICATION

Improvements in or relating to Therapeutically Useful Pyrimidine Compounds

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company (communication from Burroughs Wellcome & Co. (U.S.A.) Inc., Main Street, Tuckahoe 7, New York, in the County of Westchester, State of New York, United States of America, a Corporation organised under the laws of the State of New York, United States of America), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

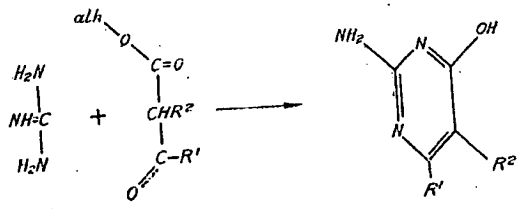
The present invention relates to a new group of aminopyrimidines which possess outstanding physiological properties in veterinary medicine and are believed to have application in the treatment of certain human ailments. These new compounds are specifically active in inhibiting the growth and spread of tumor of the type involving uncontrolled cell growth in the system. The derivatives have been discovered also to be active agents for inhibiting the growth and multiplication of certain virus of the type susceptible to rapid multiplication and growth.

The physiologically active compounds of the present invention may be graphically represented by the formula



wherein R^1 is a benzyl or an aryl radical, for example a naphthyl, phenyl, chlorophenyl, bromophenyl or nitrophenyl radical R^2 is hydrogen or a benzyl radical or a straight or branched chain alkyl radical having not more than 7 carbon atoms, and R^3 is hydrogen or a straight or branched chain alkyl radical having not more than 7 carbon atoms or a tolyl, benzyl, phenyl, chlorophenyl, bromophenyl, methoxyphenyl or ethoxyphenyl radical.

The compounds of the present invention may be conveniently synthesised by the initial preparation of the corresponding 4-hydroxy derivative by refluxing an alcoholic solution of guanidine carbonate with a selected keto ester until the reaction is complete. This reaction may be represented as follows:—

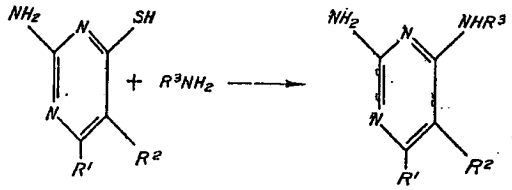


wherein R^1 and R^2 are as hereinbefore defined. The 4-hydroxy derivative is recovered by aqueous dilution and acidification of the reaction mixture in the usual manner.

The hydroxy aminopyrimidine may

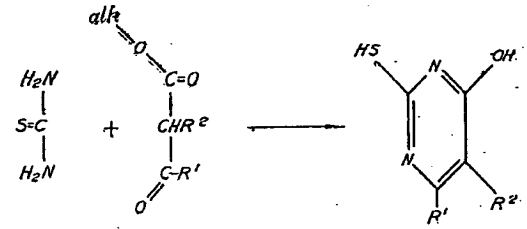
then be converted to the corresponding chloro derivative by treatment with excess phosphoryl chloride under reflux conditions. The 4-chloroaminopyrimidine is then reacted with ammonia or an amine R^3NH_2. For this purpose water, alcohol or mixtures thereof are suitable solvents. The base is usually employed in considerable excess as will be seen from the examples and, in the case of ammonia, it is convenient to use a saturated solution either in water or in alcohol.

By a somewhat modified but equally convenient procedure the above mentioned 4-hydroxy aminopyrimidine derivative can be converted into the corresponding 4-sulph-hydryl pyrimidine by methods analogous to those disclosed in Specification No. 598,514. This derivative is then transformed into the selected aminopyrimidine by methods analogous to those disclosed in the specifications of Patent Nos. 671,926 and 671,927 by drastic treatment with ammonia or an amine as follows:



The reaction proceeds smoothly with the replacement of the sulph-hydryl group by the R^3-amino group by reflux or in a sealed container depending on the nature of the amine.

By a further method the compounds may be prepared by the initial formation of a 2-sulph-hydryl-4-hydroxy pyrimidine by the reaction of a keto ester with thiourea



followed by conversion of the hydroxy group into a second sulph-hydryl group to give a 2:4-dimercaptopyrimidine. As disclosed in the specifications of Patent Nos. 671,926 and 671,927, these two groups are not of equal reactivities and ammonia or a primary amine will react with the sulph-hydryl group in the 4-position, but not that in the 2-position, to give a 2-mercapto-4-amino or 2-mercapto-4-substituted amino pyrimidine. In order to convert the sulph-hydryl group in the 2-position into an amino group, the compound may be reacted with chloracetic acid by methods analogous to those described in the specification of Patent No. 663,567 to form a 2-carboxymethyl-thio pyrimidine; this compound may now be reacted with ammonia to place an amino group in the 2-position, following the procedure described in Experiment B in said Specification No. 663,567.

The following Examples (in which the temperatures stated are on the Centigrade scale) illustrate specific methods for preparing the new derivatives in accordance with the present invention.

EXAMPLE 1.

2,4-DIAMINO-6-PHENYLPYRIMIDINE.

6-Phenylisocytosine (8 g.) was refluxed with phosphorus oxychloride (40 ccs.) for 2 hours. The excess phosphorus oxychloride was removed *in vacuo* and the semi solid residue dissolved in acetone and poured on to ice. The mixture was made alkaline with ammonium hydroxide solution and the precipitate filtered off (5 g.). On recrystallisation from aqueous ethanol 2-amino-4-chloro - 6 - phenylpyrimidine formed pale yellow needles having a melting point of 148°.

The above chloro compound (10 g.) was heated at 120—130° with 100 ccs. of ethanol saturated with ammonia at room temperature over night. The ethanol and the ammonia were evaporated and the residue treated with 4N potassium hydroxide. The solid (8 g.) was filtered.

After recrystallisation from ethanol water it formed plates having a melting point of 162°.

EXAMPLE 2.

2,4-DIAMINO-5-METHYL-6-PHENYLPYRIMIDINE.

Ethyl alpha-methylbenzoylacetate (10 g.) was refluxed with guanidine carbonate (6 g.) in alcohol (20 cc.) for 5 hours. The mass was diluted with water and then made acid with acetic acid. The crystalline mass was filtered off (5.0 g.). After recrystallisation from aqueous ethanol 2 - amino - 4 - hydroxy - 5 - methyl - 6-phenyl pyrimidine melted at 287°.

The above compound (5 g.) was refluxed with phosphorus oxychloride (35 cc.) for 1½ hours. The excess phosphorus chloride was removed *in vacuo* and the residue poured on to ice and ammonia. After recrystallisation from aqueous ethanol 2-amino - 4 - chloro - 5 - methyl - 6 - phenylpyrimidine formed plates melting at 127—128°.

The chloro compound (2.5 g.) was heated at 130—140° with a 50 cc. saturated solution of alcoholic ammonia for 20 hours. Working up in the usual manner gave the product which on recrystallisation from ethanol formed colourless needles having a melting point of 196—197°.

EXAMPLE 3.

2,4-DIAMINO-5-*n*-PROPYL-6-PHENYLPYRIMIDINE.

Ethyl alpha - *n* - propylbenzoylacetate (47 g.) was refluxed with guanidine carbonate (18.2 g.) in alcohol (200 cc.) for 6 hours. At the end of this time the mixture was poured into water, made acid with acetic acid and the solid filtered (12 g.). After crystallisation from ethanol 2 - amino - 4 - hydroxy - 5 - *n* - propyl-6-phenylpyrimidine formed flat needles having a melting point of 311—313° (decomposed).

The above amino-oxy compound (10 g.) was refluxed with phosphorus oxychloride (50 ccs.) until all was dissolved and then worked up in the usual manner. The above crude chloro compound was dissolved in 100 ccs. saturated ethanolic ammonia, heated in a closed system and worked up in the usual manner. The product (3 g.) was recrystallised from aqueous ethanol and then had a melting point of 165—166° as needles.

EXAMPLE 4.

2,4-DIAMINO-5-BENZYL-6-PHENYLPYRIMIDINE.

Ethyl alpha-benzylbenzoylacetate (40 g.) and guanidine carbonate (12 g.) in alcohol (100 ccs.) were refluxed for 12 hours. The whole was poured into water. The resulting sticky mass on removal of an oily portion with ether gave 17 gms. of crystalline material. The 2-amino-4-hydroxy - 5 - benzyl-6-phenylpyrimidine formed colourless plates on recrystallisation from ethanol having a melting point of 334° (decomposed).

The above aminohydroxypyrimidine (15 g.) was refluxed for 1 hour with phosphorus oxychloride (50 ccs.). The excess phosphorus oxychloride was removed *in vacuo* and the residue poured on to ice. After making alkaline with ammonia in the usual manner the solid was filtered and dried. It weighed 10 g.

The chloro compound (10 g.) was heated with saturated alcoholic ammonia (100 ccs.) at 130—140° overnight. The alcohol and ammonia were removed and the residue after treatment with 5N NaOH was recrystallised from aqueous ethanol giving a product (6 g.) having a melting point of 222—223°.

EXAMPLE 5.

2,4-DIAMINO-6-*p*-CHLOROPHENYL-PYRIMIDINE.

Ethyl *p*-chlorobenzoylacetate (20 g.) was refluxed with guanidine carbonate (11 g.) in alcohol (20 cc.) on a steam bath for 16 hours. The solution was poured into water acidified with acetic acid and filtered. The solid was washed with ethanol and ether (13.5 g.). After recrystallisation from acetic acid 2-amino - 4 - hydroxy - 6 - *p* - chlorophenylpyrimidine melted at 344—347° with decomposition.

The pyrimidine (11 g.) was refluxed with phosphorus oxychloride (60 ccs.) for 2 hours. In the early stages it was necessary to agitate the mixture to prevent charring. The chloro compound was worked up in the usual manner. It was heated with ethanolic ammonia (saturated) at 120—130° for 20 hours. After working up in the usual manner the diamino-pyrimidine was recrystallised from aqueous ethanol. It formed colourless needles, melting point 161—162°.

EXAMPLE 6.

2,4-DIAMINO-5-METHYL-6-*p*-CHLOROPHENYLPYRIMIDINE.

Ethyl alpha-methyl - *p* - chlorobenzoylacetate (16 g.) was refluxed with guanidine carbonate (10 g.) in alcohol 30 ccs. for 6 hours. The mixture was poured into water acidified with acetic acid and filtered. The solid weighed 13 gms. 2-Amino-4-hydroxy-5-methyl-6-*p*-chlorophenylpyrimidine was recrystallised from ethanol water and melted at 331—333°.

The hydroxy pyrimidine (13 g.) was chlorinated in the usual manner giving 14 g. of the crude chloro compound. As in the previous Examples this was heated

with alcoholic ammonia at 130°. It yielded 8 g. of the product which crystallised from ethanol water as long colourless needles having a melting point of 184—185°.

EXAMPLE 7.
2,4-DIAMINO-6-*p*-NITROPHENYL-PYRIMIDINE.

Ethyl *p*-nitrobenzoylacetate (52 g.) was refluxed with guanidine carbonate (20 g.) in alcohol (100 ccs.) The solution was acidified with acetic acid giving a yellow precipitate. The yellow precipitate was filtered and recrystallised from acetic acid. The 2-amino-4-hydroxy-6-*p*-nitrophenylpyrimidine formed small yellow needles having a melting point of 334° (decomposed).

The above aminohydroxy compound was chlorinated and aminated exactly as in the above examples. It gave the diamino compound which recrystallised from ethanol as needles having a melting point of 239° (decomposed).

EXAMPLE 8.
2,4-DIAMINO-6-BETA-NAPHTHYL-PYRIMIDINE.

Ethyl beta-naphthoylacetate (45.3 g.) was refluxed with guanidine carbonate (19 g.) in alcohol (50 cc.) for 20 hours. The solution was poured into water and acidified with acetic acid. The 2-amino-4-hydroxy-6-beta-naphthylpyrimidine was filtered and washed with ethanol and ether to give a yield of 30 g. The compound was purified by solution in 2N sodium hydroxide and precipitation with acetic acid.

This compound was chlorinated and aminated as in the preceding examples and on recrystallisation from ethanol water formed diamond-shaped plates having a melting point of 205—206°.

EXAMPLE 9.
2-AMINO-4-METHYLAMINO-6-BETA-NAPHTHYLPYRIMIDINE.

Was prepared exactly as in the preceding example except that a 25% aqueous solution of methylamine was used in place of alcoholic ammonia. It crystallised from aqueous methanol in colourless needles having a melting point of 238—239°.

EXAMPLE 10.
2-AMINO-4-METHYLAMINO-6-PHENYLPYRIMIDINE.

Was prepared from 2-amino-4-chloro-6-phenylpyrimidine exactly as above. On recrystallisation from water it melted at 195—196° and formed small needles.

EXAMPLE 11.
2-AMINO-4-ANILINO-6-PHENYL-PYRIMIDINE.

2 - Amino - 4 - chloro - 6 - phenylpyrimidine (8 g.) was refluxed with aniline (4 g.) in glacial acetic acid for 1 hour. On cooling, the acetate separated in almost quantitative yield and on recrystallisation from acetic acid gave a crystalline material having a melting point of 305—306° (decomposed).

EXAMPLE 12.
2-AMINO-4-*p*-CHLOROANILINO-6-PHENYLPYRIMIDINE.

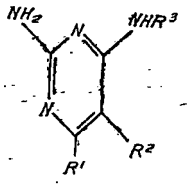
Was prepared as in the previous example. After recrystallisation from acetic acid it melted at 304—305°.

EXAMPLE 13.
2-AMINO-4-*p*-METHOXYANILINO-6-PHENYLPYRIMIDINE.

Was prepared as above; it crystallised from acetic acid as yellow prisms melting at 259—263°.

What we claim is:—

Aminopyrimidines characterised by the formula



wherein R^1 is a benzyl or an aryl radical, for example a naphthyl, phenyl, chlorophenyl, bromophenyl or nitrophenyl radical, R^2 is hydrogen or a benzyl radical or a straight or branched chain alkyl radical having not more than 7 carbon atoms, and R^3 is hydrogen or a straight or branched chain alkyl radical having not more than 7 carbon atoms or a tolyl, benzyl, phenyl, chlorophenyl, bromophenyl, methoxyphenyl or ethoxyphenyl radical.

R. F. HASLAM,
Agent for the Applicants.

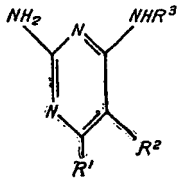
PROVISIONAL SPECIFICATION

Improvements in or relating to Therapeutically Useful Pyrimidine Compounds

We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, a British Company (communication from Burroughs Wellcome & Co. (U.S.A.) Inc., Main Street, Tuckahoe 7, New York, in the County of Westchester, State of New York, United States of America, a Corporation organised under the laws of the State of New York, United States of America), do hereby declare the nature of this invention to be as follows:—

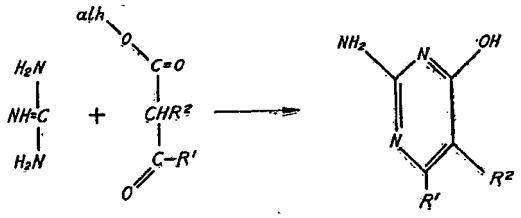
The present invention relates to a new group of aminopyrimidines which possess outstanding physiological properties in veterinary medicine and are believed to have application in the treatment of certain human ailments. These new compounds are specifically active in inhibiting the growth and spread of tumor of the type involving uncontrolled cell growth in the system. The derivatives have been discovered also to be active agents for inhibiting the growth and multiplication of certain virus of the type susceptible to rapid multiplication and growth.

The physiologically active compounds of the present invention may be graphically represented by the formula



wherein R^1 is a benzyl or an aryl radical which may be a naphthyl, phenyl, chlorophenyl, bromophenyl or nitrophenyl radical, R^2 is hydrogen or a benzyl radical or a straight or branched chain alkyl radical having not more than 7 carbon atoms, and R^3 is hydrogen or a straight or branched chain alkyl radical having not more than 7 carbon atoms or a tolyl, benzyl, phenyl, chlorophenyl, bromophenyl, methoxyphenyl or ethoxyphenyl radical.

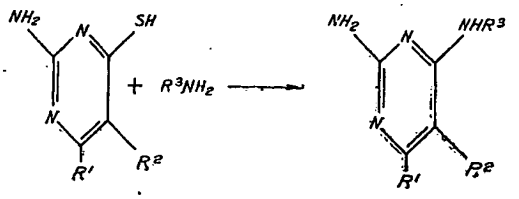
The compounds of the present invention may be conveniently synthesised by the initial preparation of the corresponding 4-hydroxy derivative by refluxing an alcoholic solution of guanidine carbonate with a selected keto ester until the reaction is complete. This reaction may be represented as follows:—



wherein R^1 and R^2 are as hereinbefore defined. The 4-hydroxy derivative is recovered by aqueous dilution and acidification of the reaction mixture in the usual manner.

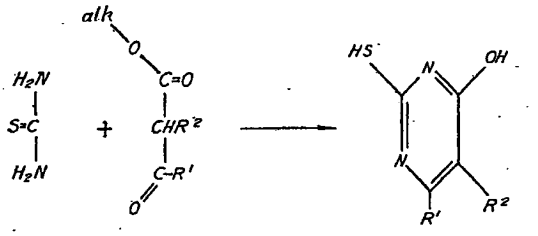
The hydroxy aminopyrimidine may then be converted to the corresponding chloro derivative by treatment with excess phosphoryl chloride under reflux conditions. The 4-chloroaminopyrimidine is then reacted with ammonia or an R^3 amine. For this purpose water, alcohol or mixtures thereof are suitable solvents. The base is usually employed in considerable excess as will be seen from the examples and, in the case of ammonia, it is convenient to use a saturated solution either in water or in alcohol.

By a somewhat modified but equally convenient procedure the above mentioned 4-hydroxy aminopyrimidine derivative can be converted into the corresponding 4-sulph-hydryl pyrimidine by the method disclosed in Specification No. 598,514. This derivative is then transformed into the selected aminopyrimidine by the methods described in the Specifications of Patent Nos. 671,926 and 671,927 by drastic treatment with ammonia or an amine as follows:—



The reaction proceeds smoothly with the replacement of the sulph-hydryl group by the R^3-amino group by reflux or in a sealed container depending on the nature of the amine.

By a further method the compounds may be prepared by the initial formation of a 2 - sulph - hydryl - 4 - hydroxy pyrimidine by the reaction of a keto ester with thiourea



followed by a conversion of the hydroxy group into a second sulph-hydryl group and the desired aminopyrimidine prepared by the methods of the said copending applications with ammonia or a selected R^3-amine.

The following Examples (in which the temperatures stated are on the Centigrade scale) illustrate specific methods for preparing the new derivatives in accordance with the present invention.

EXAMPLE 1.

2,4-DIAMINO-6-PHENYLPYRIMIDINE.

6-Phenylisocytosine (8 g.) was refluxed with phosphorus oxychloride (40 ccs.) for 2 hours. The excess phosphorus oxychloride was removed *in vacuo* and the semi solid residue dissolved in acetone and poured on to ice. The mixture was made alkaline with ammonium hydroxide solution and the precipitate filtered off (5 g.). On recrystallisation from aqueous ethanol 2 - amino - 4 - chloro-6-phenylpyrimidine formed pale yellow needles having a m.p. of 148°.

The above chloro compound (10 g.) was heated at 120—130° with 100 ccs. of ethanol saturated with ammonia at room temperature over night. The ethanol and the ammonia were evaporated and the residue treated with 4N potassium hydroxide. The solid (8 g.) was filtered. After recrystallisation from ethanol water it formed plates having a m.p. of 162°.

EXAMPLE 2.

2,4-DIAMINO-5-METHYL-6-PHENYLPYRIMIDINE.

Ethyl alpha-methylbenzoylacetate (10 g.) was refluxed with guanidine carbonate (6 g.) in alcohol (20 ml.) for 5 hours. The mass was diluted with water and then made acid with acetic acid. The crystalline mass was filtered off (5.0 g.). After recrystallisation from aqueous ethanol 2-amino-4-hydroxy-5-methyl-6-phenyl pyrimidine melted at 287°.

The above compound (5 g.) was refluxed with phosphorus oxychloride (35 cc.) for 1½ hours. The excess phosphorus chloride was removed *in vacuo* and the residue poured on to ice and ammonia. After recrystallisation from aqueous ethanol 2-amino - 4 - chloro - 5 - methyl - 6-phenylpyrimidine formed plates melting at 127—128°.

The chloro compound (2.5 g.) was heated at 130—140° with a 50 cc. saturated solution of alcoholic ammonia for 20 hours. Working up in the usual manner gave the product which on recrystallisation from ethanol formed colourless needles having a m.p. of 196—197°.

EXAMPLE 3.

2,4-DIAMINO-5-*n*-PROPYL-6-PHENYLPYRIMIDINE.

Ethyl alpha - *n* - propylbenzoylacetate (47 g.) was refluxed with guanidine carbonate (12 g.) in alcohol (200 cc.) for

6 hours. At the end of this time the mixture was poured into water, made acid with acetic acid and the solid filtered (12 g.). After crystallisation from ethanol 2-amino - 4 - hydroxy - 5 - *n* - propyl - 6-phenylpyrimidine formed flat needles having a m.p. of 311—313° (decomposed).

The above amino-oxy compound (10 g.) was refluxed with phosphorus oxychloride (50 ccs.) until all was dissolved and then worked up in the usual manner. The above crude chloro compound was dissolved in 100 ccs. saturated ethanolic ammonia, heated in a closed system and worked up in the usual manner. The product (3 g.) was recrystallised from aqueous ethanol and then had a m.p. of 165—166° as needles.

EXAMPLE 4.

2,4-DIAMINO-5-BENZYL-6-PHENYLPYRIMIDINE.

Ethyl alpha-benzylbenzoylacetate (40 g.) and guanidine carbonate (12 g.) in alcohol (100 ccs.) were refluxed for 12 hours. The whole was poured into water. The resulting sticky mass on removal of an oily portion with ether gave 17 gms. of crystalline material. The 2-amino-4 - hydroxy - 5 - benzyl - 6 - phenylpyrimidine formed colourless plates on recrystallisation from ethanol having a m.p. of 334° (decomposed).

The above aminohydroxypyrimidine (15 g.) was refluxed for 1 hour with phosphorus oxychloride (50 ccs.). The excess phosphorus oxychloride was removed *in vacuo* and the residue poured on to ice. After making alkaline with ammonia in the usual manner the solid was filtered and dried. It weighed 10 g.

The chloro compound (10 g.) was heated with saturated alcoholic ammonia (100 ccs.) at 130—140° overnight. The alcohol and ammonia were removed and the residue after treatment with 5N NaOH was recrystallised from aqueous ethanol giving a product (6 g.) having a m.p. of 222—223°.

EXAMPLE 5.

2,4-DIAMINO-6-*p*-CHLOROPHENYL-PYRIMIDINE.

Ethyl *p*-chlorobenzoylacetate (20 g.) was refluxed with guanidine carbonate (11 g.) in alcohol (20 cc.) on a steam bath for 16 hours. The solution was poured into water acidified with acetic acid and filtered. The solid was washed with ethanol and ether (13.5 g.) After recrystallisation from acetic acid 2-amino - 4 - hydroxy - 6 - *p* - chlorophenylpyrimidine melted at 344—347° with decomposition.

The pyrimidine (11 g.) was refluxed with phosphorus oxychloride (60 ccs.) for 2 hours. In the early stages it was necessary to agitate the mixture to prevent charring. The chloro compound was worked up in the usual manner. It was heated with ethanolic ammonia (saturated) at 120—130° for 20 hours. After working up in the usual manner the diamino-pyrimidine was recrystallised from aqueous ethanol. It formed colourless needles m.p. 161—162°.

EXAMPLE 6.

2,4-DIAMINO-5-METHYL-6-*p*-CHLOROPHENYLPYRIMIDINE.

Ethyl alpha-methyl - *p* - chlorobenzoylacetate (16 g.) was refluxed with guanidine carbonate (10 g.) in alcohol 30 ccs. for 6 hours. The mixture was poured into water, acidified with acetic acid and filtered. The solid weighed 13 gms. 2-Amino-4-hydroxy-5-methyl-6-*p*-chlorophenylpyrimidine was recrystallised from ethanol water and melted at 331—333°.

The hydroxy pyrimidine (13 g.) was chlorinated in the usual manner giving 14 g. of the crude chloro compound. As in the previous Examples this was heated with alcoholic ammonia at 130°. It yielded 8 g. of the product which crystallised from ethanol water as long colourless needles having a m.p. of 184—185°.

EXAMPLE 7.

2,4-DIAMINO-6-*p*-NITROPHENYL-PYRIMIDINE.

Ethyl *p*-nitrobenzoylacetate (52 g.) was refluxed with guanidine carbonate (20 g.) in alcohol (100 ccs.). The solution was acidified with acetic acid giving a yellow precipitate. The yellow precipitate was filtered and recrystallised from acetic acid. The 2-amino-4-hydroxy-6-*p*-nitrophenylpyrimidine. Formed small yellow needles having a m.p. of 334° (decomposed).

The above aminohydroxy compound was chlorinated and aminated exactly as in the above examples. It gave the diamino compound which recrystallised from ethanol as needles having a m.p. of 239° (decomposed).

EXAMPLE 8.

2,4-DIAMINO-6-BETA-NAPHTHYL-PYRIMIDINE.

Ethyl beta-naphthoylacetate (45.3 g.) was refluxed with guanidine carbonate (19 g.) in alcohol (50 cc.) for 20 hours. The solution was poured into water and acidified with acetic acid. The 2-amino-4-hydroxy-6-beta-naphthylpyrimidine was filtered and washed with ethanol and ether to give a yield of 30 g. The compound was purified by solution in 2N sodium hydroxide and precipitation with acetic acid.

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Was prepared from 2-amino-4-chloro-6-phenylpyrimidine exactly as above. On recrystallisation from water it melted at 195—196° and formed small needles.

EXAMPLE 11.

2-AMINO-4-ANILINO-6-PHENYL-PYRIMIDINE.

2 - Amino - 4 - chloro - 6 - phenylpyrimidine (8 g.) was refluxed with aniline (4 g.) in glacial acetic acid for 1 hour. On cooling, the acetate separated in almost quantitative yield and on recrystallisation from acetic acid gave a crystalline material having a m.p. of 305—306° (decomposed).

EXAMPLE 12.

2-AMINO-4-*p*-CHLOROANILINO-6-PHENYLPYRIMIDINE.

Was prepared as in the previous example. After recrystallisation from acetic acid it melted at 304—305°.

EXAMPLE 13.

2-AMINO-4-*p*-METHOXYANILINO-6-PHENYLPYRIMIDINE.

Was prepared as above; it crystallised from acetic acid as yellow prisms melting at 259—263°.

Dated this 14th day of September, 1949.

R. F. HASLAM,
Agent for the Applicants.

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